# Continuous combined hormone replacement therapy and risk of endometrial cancer

**Deirdre A. Hill, PhD,[a, c] Noel S. Weiss, MD, DrPH,[a, c] Shirley A.A. Beresford, PhD,[a, c] Lynda F. Voigt, PhD,[c] Janet R. Daling, PhD,[a, c] Janet L. Stanford, PhD,[a, c] and Steve Self, PhD[b, c]**

*Seattle, Washington*

**OBJECTIVE:** Postmenopausal women who receive sequential hormone replacement therapy with estrogen combined with progestogen for 10 to 24 d/mo for a prolonged period may have an elevated endometrial cancer risk relative to those who have never received hormone replacement therapy. We investigated whether daily use of estrogen and progestogen (continuous combined hormone replacement therapy) could diminish any excess endometrial cancer risk.

**STUDY DESIGN:** A population-based study in Washington State obtained interview data from 969 women aged 45 to 74 years with endometrial cancer diagnosed during 1985 through 1991 or 1994 through 1995 and from 1325 age-matched control subjects selected primarily by random digit dialing. Women who had received only continuous combined hormone replacement therapy were compared with women who had only received another hormone replacement therapy regimen or who had never received hormone replacement therapy.

**RESULTS:** The risk of endometrial cancer among users of continuous combined hormone replacement therapy (n = 9 case patients, n = 33 control subjects) relative to women who had never received hormone replacement therapy was 0.6 (95% confidence interval, 0.3-1.3); the risk relative to women who received hormone replacement that included progestogen for 10 to 24 d/mo was 0.4 (95% confidence interval, 0.2-1.1). Most continuous combined hormone replacement therapy use was short-term (<72 months) or recent (in the previous 24 months).

**CONCLUSION:** Women who had received continuous combined hormone replacement therapy for several years did not appear to be at any increased risk for endometrial cancer relative to women who had never received hormone replacement therapy and may in fact be at decreased risk for endometrial cancer. (Am J Obstet Gynecol 2000;183:1456-61.)

**Key words:** Endometrial neoplasms, estrogen replacement therapy, estrogens, menopause, progestational hormones

Hormone replacement therapy is an efficacious means of lowering risk of fractures among postmenopausal women and may be efficacious in lowering risk of cardiovascular disease.[1-5] Women seek out hormone replacement therapy and physicians recommend it for these reasons and also for the relief of menopausal symptoms. Use of estrogen alone for menopausal treatment is associated with the proliferation of endometrial cells,[6] hyperplasia,[7, 8] and the development of endometrial cancer.[9] However, addition of a progestogen to the estrogen regimen for a number of days per month, known as *sequential hormone replacement therapy,* reduces these risks,[7, 8, 10-12] and this therapy is now commonly used for women who have not had a hysterectomy.

Although women whose therapy includes a progestogen component for <10 d/mo have a reduced risk of endometrial cancer relative to those who receive estrogen alone, their risk is still elevated relative to women who have never received hormone replacement therapy. Whereas women whose regimens include progestogen for 10 to 24 d/mo have a lower risk of endometrial cancer than those whose therapy includes progestogen for fewer days,[10] long-term use of such a regimen has nonetheless (in 2 of 3 studies[13-15]) been associated with a moderate increase in risk relative to that of women who have not received hormone replacement therapy. The number of days per month of progestogen necessary to eliminate an increased risk relative to nonusers of hor-

*From the Department of Epidemiology[a] and the Department of Biostatistics,[b] University of Washington, and the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center.[c]*

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*Reprint requests: Deirdre A. Hill, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, MSC 7238, Bethesda, MD 20892-7238.*



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mones is not clear. The inverse relationship between days per month of progestogen use and endometrial cancer risk suggests the possibility that daily use of progestogen with estrogen therapy, known as *continuous combined hormone replacement therapy,* might be associated with a further decrease in risk. Continuous combined hormone replacement therapy has shown promise as a regimen that does not increase risk of endometrial hyperplasia with short-term use,[7, 8] but the risk of endometrial cancer among women who use this regimen has as yet received little investigation. This study was undertaken to examine the risk of endometrial cancer among women who received continuous combined therapy relative both to other hormone replacement therapy regimens and to no therapy.

## Material and methods

Female residents of one of three counties of western Washington State who had endometrial cancer diagnosed during 1985 through 1991 or 1994 through 1995 were identified by the Cancer Surveillance System, a population-based cancer registry. Women who had endometrial cancer diagnosed during 1985 and 1986 were included in the study if they were residents of King County and were 45 to 64 years of age. Women residing in King, Pierce, and Snohomish counties were eligible if they had endometrial cancer diagnosed during 1987 through 1990 and were 45 to 74 years of age, or they had endometrial cancer diagnosed during 1991 and were 45 to 69 years of age. For 1994 through 1995 recruitment was limited to King County women aged 50 to 69 years.

Of the 1436 identified case patients, 114 were found to be ineligible: 72 women had a nonepithelial or in situ tumor, and 42 women were excluded because of communication difficulties, ineligible residences, or unavailability of a telephone at the time of diagnosis. Among the remaining 1322 eligible case patients, 109 died before interview, 244 were not interviewed because of physician or subject refusal, and 1 interview was lost. A total of 969 women (73.3%) were interviewed, 832 of whom had endometrial cancer diagnosed between 1985 and 1991 and 137 of whom had endometrial cancer diagnosed between 1994 and 1995. Details of case patient recruitment for 1985 through 1991 have been published previously elsewhere.[10, 13]

Random digit dialing[16] was used to identify all control subjects for the years 1985 to 1991 and 31% of control subjects for the reference years 1994 and 1995. Control subjects selected by random digit dialing were matched to case patients by county of residence and by 5-year age group. Of the 2777 women found to be eligible for the study, 2040 (73.5%) agreed to an interview. Included in this analysis are the 1179 control subjects who neither had a hysterectomy at ≥6 months before the reference date nor had previous endometrial cancer.

For 1994 and 1995 there were 2 additional sources of control subjects—a 1.0% random sample of female King County residents aged 65 through 69 years was drawn each year from the files of the Health Care Financing Administration, and a subsample served as control subjects for case patients in the same age group with endometrial cancer diagnosed that year. Of the 128 women contacted who were identified through the Health Care Financing Administration 63 (49.2%) were found to be ineligible, 8 refused but had not had a hysterectomy (6.3%), and an additional 8 were deceased, refused, or could not be located, and their hysterectomy status was unknown (6.3%). Interviews were obtained with 49 women (75.4%). Residents of King County who participated as control subjects in the multicenter Contraceptive and Reproductive Experience study were also included in this study if they were aged 50 to 64 years, had an interview reference date in 1994 or 1995, and had not had a hysterectomy. Among the 127 eligible women who were contacted with random digit dialing for the Contraceptive and Reproductive Experience study, 97 women (76.4%) were interviewed, 8 (6.3%) refused but were known to not have had a hysterectomy, and 22 refused with hysterectomy status unknown (17.3%). The Health Care Financing Administration and the Contraceptive and Reproductive Experience study were the sources of 23% and 46% of the control subjects, respectively, for case patients with endometrial cancer diagnosed in 1994 and 1995.

Each control subject was assigned a reference date, analogous to the date of endometrial cancer diagnosis among the case patients, and all interviews collected data regarding the experiences of case patients and control subjects before the reference date or date of diagnosis. Control subject reference years were assigned to approximate the year of diagnosis among the case patients, and within a given reference year a reference month was assigned at random for each woman. This study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center, Seattle.

After they provided informed consent, study subjects were interviewed in person by trained interviewers, except for 2.9% of case patients and 4.2% of control subjects who were interviewed by telephone. Reproductive and medical history data until the month of diagnosis (case patients) or reference date (control subjects) were collected, as were routine demographic data. A detailed history of medication use, including use of contraceptive and noncontraceptive hormones, was obtained by providing photographs of common medications and a life events calendar to aid recall. Subjects interviewed by telephone received photographs of hormonal preparations by mail before the interview.

The reason for hormone use was assessed, blinded to case-control status, by reviewing information provided by the study participants. In the analysis hormone ther-

**Table I.** Characteristics of case patients with endometrial cancer and control subjects

| Characteristic | *Case patients (n = 969)* | | *Control subjects (n = 1325)* | |
|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* |
| Age | | | | |
| 45-54 y | 192 | 19.8 | 379 | 28.6 |
| 55-64 y | 424 | 43.8 | 607 | 45.8 |
| 65-74 y | 353 | 36.4 | 339 | 25.6 |
| Race | | | | |
| White | 936 | 96.6 | 1256 | 94.8 |
| Nonwhite | 33 | 3.4 | 69 | 5.2 |
| Education | | | | |
| ≤12 y | 459 | 47.4 | 546 | 41.2 |
| 13-16 y | 426 | 44.0 | 644 | 48.6 |
| ≥17 y | 83 | 8.5 | 134 | 10.1 |
| Missing data | 1 | 0.1 | 1 | 0.1 |
| No. of births | | | | |
| 0 | 159 | 16.4 | 136 | 10.3 |
| 1 | 112 | 11.6 | 134 | 10.1 |
| ≥2 | 698 | 72.0 | 1055 | 79.6 |
| Body mass index | | | | |
| ≤21.7 kg/m$^2$ | 189 | 19.5 | 335 | 25.3 |
| 21.8-24.0 kg/m$^2$ | 178 | 18.4 | 316 | 23.8 |
| 24.1-27.5 kg/m$^2$ | 210 | 21.7 | 359 | 27.1 |
| ≥27.6 kg/m$^2$ | 389 | 40.1 | 311 | 23.5 |
| Missing data | 3 | 0.3 | 4 | 0.3 |
| Use of oral contraceptives | | | | |
| Never | 651 | 67.2 | 761 | 57.4 |
| Ever | 318 | 32.8 | 564 | 42.6 |
| Cigarette smoking | | | | |
| Never | 531 | 54.8 | 586 | 44.2 |
| Ever | 279 | 28.8 | 448 | 33.8 |
| Current | 159 | 16.4 | 291 | 22.0 |
| Date of diagnosis or reference | | | | |
| 1985-1987 | 236 | 24.4 | 270 | 20.4 |
| 1988-1991 | 596 | 61.5 | 844 | 63.7 |
| 1994-1995 | 137 | 14.1 | 211 | 15.9 |

apy use was restricted to that judged to be used for menopause-related reasons. Use of hormones solely for regulation of menstruation or for depression, anxiety, or emotional distress was not included as hormone replacement therapy use unless this use occurred around the age that a woman reported natural menopause or the hormones were used continuously through the age of 45 years or initiated any time after the age of 45 years. Hormonal treatment only for infertility or other conditions not related to menopause was classified as nonuse of hormone replacement therapy. Women who had never received any menopausal hormone therapy or had received such therapy for <6 months were considered never to have used hormone replacement therapy. Because women who have used more than 1 hormone regimen may have a risk of endometrial cancer that is not clearly attributable to either single regimen, we restricted hormone replacement therapy users in the analysis to women who had primarily received only 1 hormone replacement therapy regimen. Users of each hormone schedule or regimen were defined as women who had received that hormone regimen for ≥6 months and had not used any other regimen for ≥6 months. Thus the unopposed estrogen use group was limited to women who had received that therapy for ≥6 months and had at most received only short-term therapy (<6 months) with other regimens. Each group of hormone replacement therapy users was delineated similarly as users of only 1 regimen if total use of other regimens was for <6 months. Women who had received estrogen with an added progestogen in a sequential or combined regimen for <10 d/mo were considered separately in the analysis from women who had received estrogen combined with progestogen for 10 to 24 d/mo. Women who had received estrogen with an added progestogen for ≥25 d/mo were considered to have received continuous combined hormone replacement therapy. All women who had used 1 of the 4 described regimens in the form of either pills or percutaneous skin patches, or both, were included in the analysis (patch use represented <2% of total). Because progestogen or combined skin patches were not marketed in the United States during this time period, a sequential patch user was categorized by the number of days per month that she took progestogen pills during the period that she was wearing an estrogen patch. Women who had used for ≥6 months any nonoral or nonpatch hormone therapy, including creams, injections, liquids, gels, and intrauterine contraceptive devices or who used progestogens or androgens alone were also excluded. In all, these criteria led to the exclusion of 384 women (16.9%), which left a total of 788 case patients and 1122 control subjects for analysis.

Factors evaluated as potential confounding variables included demographic variables, factors known or suspected to be related to endometrial cancer, and estrogen and progestogen doses among hormone replacement therapy users. Unconditional logistic regression was used to compute odds ratios and associated 95% confidence intervals for the relationship between hormone therapy use and endometrial cancer and to evaluate possible confounding of this relationship by other factors.

All analyses were adjusted for the 2 variables that were found to alter the logistic regression estimate by ≥10%—reference age (in years) and body mass index (≤27.4 kg/m$^2$ vs >27.4 kg/m$^2$). No additional control of confounding by body mass index was achieved with a finer categorization. A few questions were worded differently during 1985 through 1991 than in subsequent years (income, weight), and we therefore also adjusted for reference period (1985-1991 vs 1994-1995). In addition, duration of hormone use (in months) was taken into account in analyses that compared 2 regimens of hormone therapy. Few tumors were diagnosed at other than stage I, and we therefore examined simply whether disease was confined to the endometrium or extended beyond it.

**Table II.** Endometrial cancer risk among women who receive continuous combined hormone replacement therapy as compared with users of other hormone therapies or no therapy

| | *Case patients* | | *Control subjects* | | *Odds ratio* | |
|---|---|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* | *Adjusted** | *95% Confidence interval* |
| *Nonuse versus continuous combined hormone replacement therapy* | | | | | | |
| No hormone replacement therapy use | 392 | 97.8 | 793 | 96.0 | 1.0 | Referent |
| Continuous combined hormone replacement therapy | | | | | | |
| Ever | 9 | 2.2 | 33 | 4.0 | 0.6 | 0.3-1.3 |
| 6-36 mo | 4 | 1.1 | 16 | 2.0 | 0.6 | 0.2-1.7 |
| ≥37 mo | 5 | 1.1 | 17 | 2.0 | 0.6 | 0.2-1.8 |
| *Estrogen alone versus continuous combined hormone replacement therapy* | | | | | | |
| Estrogen alone | 314 | 97.2 | 170 | 83.7 | 1.0 | Referent |
| Continuous combined hormone replacement therapy | 9 | 2.8 | 33 | 16.3 | 0.2 | 0.1-0.5 |
| *<10 d progestogen sequential versus continuous combined hormone replacement therapy* | | | | | | |
| Sequential therapy with progesterone <10 d/mo | 33 | 78.6 | 35 | 51.5 | 1.0 | Referent |
| Continuous combined hormone replacement therapy | 9 | 21.4 | 33 | 48.5 | 0.3 | 0.1-0.8 |
| *10-24 d progestogen sequential versus continuous combined hormone replacement therapy* | | | | | | |
| Sequential therapy with progesterone 10-24 d/mo | 40 | 81.6 | 91 | 73.4 | 1.0 | Referent |
| Continuous combined hormone replacement therapy | 9 | 18.4 | 33 | 26.6 | 0.4 | 0.2-1.1 |

*Analyses were adjusted for reference year (1985-1991 and 1994-1995), age in years, and body mass index (≤27.4 kg/m$^2$ vs ≥27.5 kg/m$^2$). Comparisons between 2 hormone regimens were also adjusted for duration of hormone replacement therapy use in months.

## Results

Case patients were somewhat older than control subjects and were more likely to be nulliparous, to be of higher body mass index, and to never have smoked or used oral contraceptives (Table I). Nine women with endometrial cancer had received continuous combined hormone replacement therapy, in contrast with 33 control subjects (Table II). Compared with women who had never used hormone replacement therapy, women who had used continuous combined hormone therapy had an adjusted relative risk of endometrial cancer of 0.6 (95% confidence interval, 0.3-1.3; Table II). Risk did not appear to differ according to duration of therapy among these women, most of whom had used menopausal hormones for only a relatively short time (median duration, 39 months). Compared with users of unopposed estrogens, women who used continuous combined therapy had an 80% reduction in risk (odds ratio, 0.2; 95% confidence interval, 0.1-0.5). Users of continuous combined hormone replacement therapy had a risk that was 0.3 that of women who used a regimen that included progestogen for <10 d/mo (95% confidence interval, 0.1-0.8) and 0.4 that of women who used progestogen for 10 to 24 d/mo (95% confidence interval, 0.2-1.1).

Other information available for analysis included duration and recency of hormone use, estrogen and progestogen doses, and characteristics of the tumor, such as stage, grade, and extent of disease. All but one of the users of continuous combined hormone replacement therapy were current or recent users at the reference date (≤24 months since last use), and most had not used hormones for an extended period. We performed analyses restricted to women who were current or recent users of hormone replacement therapy or to those who had used menopausal hormones for ≤72 months. Our findings were not substantially different from those described previously. Results were also unchanged when analyses were limited to women who had received a conjugated estrogen dose of only ≤0.9 mg and among subgroups of case patients according to the grade or extent of the tumor (data not shown).

## Comment

Several limitations should be considered in the interpretation of the study results. About 26% of eligible case patients and control subjects did not participate in the study. Also, few women were past users or long-term users of any hormone regimen except unopposed estrogen. The small stratum sizes limited our power to detect differences in risk with extended combined hormone use or use that had ceased in the distant past. Differential accuracy of recall of hormone use between case patients and control subjects might have resulted in biased estimates of relative risk. However, three studies have found generally good agreement between interviews and medical records for both case patients and control subjects.[17-19] Agreement has ranged from 75% to 87% (κ, 0.51-0.74) for ever or never having used menopausal estrogen therapy, and dose and duration of use were also generally in agreement with medical charts.[17, 19] Recall may be enhanced by in-person interviews that use photographs of medications to identify brand and dose, an approach that was used in this study.[20]

We do not yet know the optimal manner in which

progestogen should be used with postmenopausal estrogens to avoid an excess risk of endometrial cancer. The incidence of endometrial hyperplasia is greater among women whose regimen includes progestogen for <10 d/mo[21] than among those whose regimen includes progestogen for a longer monthly duration.[7, 8] Women who receive a progestogen component for 10 to 24 d/mo have a lower risk of endometrial cancer than do those who receive a progestogen component for fewer days.[10, 13] In a previous study women who had used continuous combined therapy, either solely or in addition to other regimens, had a relative risk of endometrial cancer of 1.1 (95% confidence interval, 0.8-1.4) per 5 years of use.[14] In another study women who had ever received continuous combined hormone replacement therapy had an endometrial cancer risk of 0.7 (95% confidence interval, 0.4-1.0) relative to those who had never received continuous combined hormone replacement therapy.[15]

Our results suggest that women who have received continuous combined hormone replacement therapy for a relatively short period and are recent users have a risk of endometrial cancer that is not elevated with respect to that of those who have never used hormone replacement therapy. Women who received continuous combined hormone replacement therapy had a lower risk of endometrial cancer than did women who received either the unopposed estrogen regimen or added progestogen for <10 d/mo, and there was a suggestion that their risk was also lower than that of women who received added progestogen for 10 to 24 d/mo. These data provide further evidence that endometrial cancer risk decreases with increasing days per month of progestogen use. The lowered risk may not be mediated solely by the monthly renewal of the superficial layers of the endometrial epithelium, because many women who use continuous combined hormone replacement therapy do not experience the monthly bleeding common among sequential hormone replacement therapy users.[22]

Endometrial cancer risk is one element of the health risks and benefits associated with hormone replacement therapy. The reduction in fracture risk and the possible reduction in the incidence of myocardial infarction appear to be maintained only by current or recent use of menopausal estrogens,[1, 3, 4] and so many women are receiving recommendations to continue hormone replacement therapy long-term to derive these benefits.[3] Although myocardial infarction and hip fracture are associated with a higher case fatality than is endometrial cancer,[23-25] risk of cancer remains a deterrent to extended use of hormone replacement therapy for many women.[26] If endometrial cancer risk could be reduced or eliminated by daily use of progestogen without mitigating the beneficial effects of estrogen on the cardiovascular and skeletal systems, then women who seek to use hormone replacement therapy might find such regimens more acceptable for extended use. It is therefore important to determine whether the relatively low risks of endometrial cancer associated with short-term use of continuous combined hormone replacement therapy in this study will be maintained with long-term use.

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